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Facilitating direct compaction tableting of fine cohesive APIs using dry coated fine excipients: Effect of the excipient size and amount of coated silica

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ABSTRACT

The possibility of attaining direct compression (DC) tableting using silica coated fine particle sized excipients was examined for high drug loaded (DL) binary blends of APIs. Three APIs, *very-cohesive* micronized acetaminophen (mAPAP, 7 μm), *cohesive* acetaminophen (cAPAP, 23 μm), and *easy-flowing* ibuprofen (IBU, 53 μm), were selected. High DL (60 wt%) binary blends were prepared with different fine-milled MCC-based excipients (ranging 20- 37 μm) with or without A200 silica coating during milling. The blend flowability (flow function coefficient −FFC) and bulk density (BD) of the blends for all three APIs were significantly improved by 1 wt% A200 dry coated MCCs; reaching FFC of 4.28 from 2.14, 7.82 from 2.96, and > 10 from 5.57, for mAPAP, cAPAP, and IBU blends, respectively, compared to the uncoated MCC blends. No negative impact was observed on the tablet tensile strength (TS) by using dry coated MCCs despite lower surface energy of silica. Instead, the desired tablet TS levels were reached or exceeded, even above that for the blends with uncoated milled MCCs. The novelty here is that milled and silica coated fine MCCs could promote DC tableting for cAPAP and IBU blends at 60 wt% DL through adequate flowability and tensile strength, without having to dry coat the APIs. The effect of the silica amount was investigated, indicating lesser had a positive impact on TS, whereas the higher amount had a positive impact on flowability. Thus, the finer excipient size and silica amounts may be adjusted to potentially attain blend DC processability for high DL blends of fine APIs.

1. Introduction

Tablets are widely chosen for drug delivery because of their high level of stability, less expensive production and distribution costs, simple administration, and better patient compliance (Rasenack and Müller, 2002; Sam and Fokkens, 1997; Sheth et al., 1980). In recent years, the pharmaceutical industry has favored direct compression as a preferred approach for tablet manufacturing due to fewer steps compared to dry-granulation and wet granulation. However, most active pharmaceutical ingredients (APIs) cannot be compressed directly into tablets due to their inadequate bulk properties, like poor flowability, bulk density, and/or poor compactability (G Mirani et al., 2011; Vanhoorne et al., 2014). Hence excipients, often present in comparable or even higher concentrations than the API, are used to enable direct compression tableting. The direct compression blend typically requires adequate flowability, assessed by using a shear-cell based measurement of the powder flow function coefficient, FFC, of 6.8 or higher (Chen et al., 2018b; Shi et al., 2011)), bulk density (about 0.38 g/ml or higher) (Chen et al., 2019a; Shi et al., 2011), and tablet tensile strength of 1.7 MPa (Pitt and Heasley, 2013) to avoid handling and feeding issues. Specifically, criteria of bulk density and FFC are based on properties of Avicel PH-102 which is considered to be an exemplary material for direct compression via high-speed tableting (Shi et al., 2011).Thus, a FFC greater than 6.8 and tablet tensile strength greater than 1.7 MPa are proposed as the direct blending and direct compression (DB-DC) requirements. Unfortunately, most commercially available excipients fail to provide the necessary range of bulk properties as the desired API drug loading (DL), especially for fine and cohesive API, increases to about 30 wt% and higher, necessitating the need of high-functionality excipients (Chen et al., 2019b; Huang et al., 2015b; Kunnath et al., 2018; Paradkar and York, 2016). The prevalence of formulations containing APIs for improved bioavailability have particle sizes of 30 μm (D50), more

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typically below 20 μm, (Han et al., 2011; Li et al., 2015), further underscoring the need for developing specialized excipients (Chen et al., 2018b; Chen et al., 2019b). There are an increasing number of commercially available novel excipients intended to enable direct compressibility, for example, Prosolv® grade of microcrystalline cellulose (MCC) based silicified excipients; however, most have much larger sizes (>60 μm) as compared with the finer API sizes (<60 μm). Therefore, their usage may lead to downstream segregation issues, jeopardizing drug content uniformity in the direct compaction process (Jivraj et al., 2000; Rojas et al., 2012). Hence there is a need for novel excipients that are finer, e.g., < 50 μm, yet can impart higher flowability, bulk density and tablet compactability for formulations containing finer APIs at higher DL levels to facilitate direct compaction.

Excipients with enhanced functionality are not easy to develop due to physics based constraints (Rojas et al., 2012). For example, an excipient like Avicel® PH-200 having a D50 of 185 μm has excellent flowability and bulk density, achieved by its large particle size. Unfortunately, the enhanced flowability comes at the expense of compactability (Doelker et al., 1995; Lahdenpää et al., 1997). Conversely, Avicel® PH-105 having a D50 of 20 μm exhibits heightened compactability, but consequently has high level of cohesion owing to its fine particle size (Chen et al., 2018b). Interestingly, a recent work involving the creation of a fine surface-engineered excipient, achieved by coating guest particles (Aerosil 200 (A200, nano-size hydrophilic silica)) onto the surface of a host particle (Avicel PH-105 (fine-grade MCC)) (Chen et al., 2018b; Chen et al., 2019b), demonstrated significant promise towards overcoming this challenge. The A200 silica dry-coated Avicel PH-105 achieved excellent flowability and bulk density, without significant loss of tensile strength in placebo tablets. Further, it helped impart excellent flowability, bulk density, and most importantly, no loss in tensile strength for binary blends with exemplary fine APIs (<60 μm), e.g., even micronized Acetaminophen (7 μm) at up to 30 wt% drug loading and corresponding not-so-fine Acetaminophen (23 μm), also called *coarse* APAP in previous papers, at up to 60 wt% drug loading (Chen et al., 2018b; Chen et al., 2019b). In this paper, the use of term "coarse acetaminophen (cAPAP)" does not imply that it is not a fine API, but to clarify its size being larger than micronized acetaminophen (mAPAP). In contrast, commercially available MCC excipients such as Avicel 102 as well as MCC-based silicified excipient Prosolv® 50 and Prosolv® 90 were found to be unsuitable for direct blending and direct compression for such fine APIs at similar high drug loading levels (Chen et al., 2019b; Huang et al., 2015b; Kunnath et al., 2018). Remarkably, Prosolv® 50 (finer one amongst two Prosolv® sizes) shows greater tablet tensile strength than Prosolv® 90 (coarser one), although dry coated Aviel PH-105 outperformed them as well as uncoated Aviel PH-105 by achieving much greater FFC and bulk density values. These results are interesting because although finer excipients are expected to help with enhanced tablet tensile strength due to their larger specific surface area, they are not expected to lead to improved flowability of the blend due to their finer sizes. Thus, such interesting outcomes uncover unexpected utility of fine excipients that are silica coated for imparting DB-DC capability to binary formulations and warrant further investigation to assess how the combination of the excipient size and the API size impact the blends DB-DC capability.

Consequently, the focus of the present work was to investigate the effect of different sizes of fine surface engineered excipients, prepared by coating silica onto their surfaces, on the bulk properties of their binary blends with three different APIs (7, 23 and 53 μm) to attain DB-DC capability by achieving a blend FFC > 6.8, bulk density > 0.38 g/ml, and tablet tensile strength of 1.7 or higher. Four different fine-sized MCC-based excipients, range 20 μm − 37 μm, were prepared by milling Pharmacel 101 (MCC101) as a starting material, with or without simultaneous silica coating. It is noted that unless otherwise stated, the particle size referenced throughout this study is D50. Two fine sized APIs (<25 μm), micronized Acetaminophen (mAPAP) at 7 μm, and comparatively larger, but called "coarse" Acetaminophen (cAPAP) at 23 μm, and one not so fine sized API, Ibuprofen 50 (IBU), 53 μm, were considered as model APIs in preparing the binary blends due to their different flowability ranging from very cohesive (mAPAP) to barely easy flow category (IBU) (measured via shear-testing with 3 kPa pre-shear normal stress). Initially, the study examined the impact of excipient size through various arrangements and combinations of APIs and excipients based on their sizes. Subsequently, excipients with and without a fixed weight amount of silica coating were incorporated into binary blends to assess the enhancement achieved through dry coating. Lastly, a fixed percentage of surface area coverage (SAC) was introduced to elucidate the manipulation of particle size and silica amount in order to attain the desired blend properties, by adjusting the weight amount of silica. It was hypothesized that these combinations of API and excipient sizes, along with the silica amounts, would help identify their best combinations which could lead to achieving DB-DC capability for *very cohesive* (FFC < 2), *cohesive* (2 < FFC < 4), and nearly cohesive (4 < FFC < 4.5) which is at the very low end of the *easy-flow* category (4 < FFC < 10) APIs, without having to dry coat the API itself as was done in some of the previous papers (Huang et al., 2015b; Kunnath et al., 2018).

2. Materials and Methods

2.1. Materials

Microcrystalline Cellulose (MCC) Pharmacel 101 (MCC101), donated by DFE Pharma Corporation, USA, was used to prepare milled MCC powders, to be used as a filler. Aerosil A200 silica (A200), donated by Evonik Corporation, USA, was used to dry coat milled Pharmacel 101. Micronized Acetaminophen (mAPAP), coarse Acetaminophen (cAPAP), and Ibuprofen 50 (IBU) were selected as model drugs acquired or purchased from Mallinckrodt Pharmaceuticals (MO, USA), Changshu Huagang Pharmaceutical CO., Ltd (China), and BASF (NY, USA), respectively.

2.2. Preparation of multiple-component blends

2.2.1. Preparation of milled MCC powders and their simultaneous dry coating

A V-blender (Patterson-Kelley, USA) was used to prepare pre-mixed powder for subsequent dry coating, which contained MCC101 and various amounts of A200 as shown in Table 1. The blend constituents were filled into the 4-quart V-shaped blender and operated at 25 rpm for 10 mins to prepare each pre-blend. The V-shaped container can load materials up to around 400 g. Each mixing batch contained 100 g corresponding mixtures.

Either as-received MCC101 or pre-mixed MCC101 and silica powders underwent processing in a Fluid Energy Milling (FEM) unit (Sturtevant Inc., MA, USA), with the powder feeding rate controlled by a volumetric feeder (Schenck Accurate, WI, USA). Milling of as-received MCC101 produced uncoated fine-milled MCC powders and they were used in all blends containing uncoated excipients. In contrast, dry coated milled MCCs were achieved in tandem with particle size reduction in a fluid energy mill, following a pre-mixing step of the MCC101 and silica powders. The feeder was calibrated using the pre-mixed powder prior to each experiment. Detailed information regarding the experimental setup

Table 1
Summary of formulation for MCC blended with silica prior to milling.

Sample ID	MCC101% (w/w)	A200 Silica% (w/w)
MCC101 + 1 wt%A200	99.00	1.00
MCC101 + 0.82 wt%A200	99.18	0.82
MCC101 + 0.67 wt%A200	99.33	0.67
MCC101 + 0.55 wt%A200	99.45	0.55
MCC101 + 0.43 wt%A200	99.57	0.43
MCC101 + 0.4 wt%A200	99.60	0.40

Table 2
FEM process parameters, particle size, and intended surface area coverage (SAC) for dry coated and uncoated MCC.

Sample ID	Feed Material	Feed pressure (psi)	Griding pressure (psi)	Feed rate (g/min)	D10 (μm)	D50 (μm)	D50 (μm)	D32 (μm)	Intended SAC%
MCC37	MCC101	30	25	2.0	10.86	36.45	81.10	17.29	–
MCC30	MCC101	40	35	2.0	10.53	31.41	74.65	15.63	–
MCC25	MCC101	50	45	2.0	8.31	26.11	67.55	12.84	–
MCC20	MCC101	55	50	1.5	7.93	20.14	53.31	9.96	–
MCC37 + 1 wt%A200	MCC101 + 1 wt%A200	30	25	2.0	11.50	36.39	83.02	16.26	242
MCC37 + 0.67 wt%A200	MCC101 + 0.67 wt%A200	30	25	2.0	10.54	34.82	77.70	15.82	158
MCC37 + 0.43 wt%A200 (orMCC37 + 115 %SACA200)	MCC101 + 0.43 wt%A200	30	25	2.0	13.44	38.33	60.30	17.10	109
MCC37 + 0.4 wt%A200	MCC101 + 0.4 wt%A200	30	25	2.0	12.33	37.21	59.61	16.85	100
MCC30 + 1 wt%A200	MCC101 + 1 wt%A200	40	35	2.0	9.13	28.89	72.32	13.74	205
MCC25 + 1 wt%A200	MCC101 + 1 wt%A200	50	45	2.0	8.19	25.29	67.45	12.35	184
MCC20 + 1 wt%A200	MCC101 + 1 wt%A200	55	50	1.5	7.81	20.38	52.16	9.43	141
MCC30 + 115 %SACA200	MCC101 + 0.55 wt%A200	40	35	2.0	10.36	30.26	74.10	13.91	114
MCC20 + 115 %SACA200	MCC101 + 0.82 wt%A200	55	50	1.5	8.01	20.78	52.19	9.63	117

and methodology can be found in previous publications (Han et al., 2011; Kim et al., 2023). The feed rate and the grinding pressure ranged from 1.5 to 2.0 g/min and 25.0 to 50.0 psi, respectively, with the feed pressure set to 5.0 psi higher than the grinding pressure. The processed samples were securely stored in airtight plastic bags under room conditions (25 °C and 24 % relative humidity) for future investigations. The operating parameters of the FEM, as detailed in Table 2, were methodically adjusted to attain the desired particle sizes. For the cases where the pre-mixed MCC101 and silica was milled, the surface of the MCC was coated with silica, resulting in what is referred to as a "surface-engineered excipient." Scanning Electron Microscope images of specific instances are depicted in Fig. 1 to illustrate the alterations in surface morphology resulting from the coating process.

2.2.2. Binary blends preparation

A V-blender (Patterson-Kelley, USA) was used to prepare binary blends which contain one of 3 selected APIs and corresponding excipients at 60 % drug loadings. The formulation is shown in Table 3. The blends were filled into the 4-pint V-blender and operated at 25 rpm for 12 mins. Each batch contained 100 g corresponding multiple-component blends.

2.3. Binary blends characterization by FT4 powder rheometer

The bulk density and the flow function coefficient (FFC) of multiple-component blends were obtained by the Freeman Technology FT4 powder tester (Freeman Technologies Ltd., Worcestershire, UK). The FFC of blends was measured following a standard FT4 program "shear_3kPa" where a shear cell test used 3 kPa consolidation pressure. FFC was a ratio of consolidation stress to the unconfined yield stress relating to bulk flowability. The physical meaning of FFC values were interpreted as followed: FFC < 1 – not flowing, $1 <$ FFC < 2 – very cohesive, $2 <$ FFC < 4 – cohesive, $4 <$ FFC < 10 – easy flowing, and FCC > 10 – free-flowing (Schulze, 2008). Each characterization was measured in triplicates. The bulk density was tested through another standard FT4 program procedure "1C split 1 T". The inherent property of powders allows for their packing arrangement to be easily and significantly altered. Consequently, in defining density, it is crucial to accurately determine and replicate the packing state. This is accomplished through a Conditioning cycle on the FT4. With additional functionalities like the built-in balance and Split Vessels, enabling precise volume measurement, the Conditioned Bulk Density can be determined with unparalleled precision. More details and information for measurement and data analysis of bulk density and FFC could be found in previous work (Freeman, 2007; Huang et al., 2015b; Kunnath et al., 2018). Each characterization replicates 3 times.

2.4. Tableting performance

The Carver platen press (Carver, Inc., USA) was used to prepare tablets with four compaction forces (0.5, 1.0, 1.5, 2.0 metric tons, corresponding to 38, 76, 114, and 152 MPa, respectively). The dwell time was 5 s for each compaction. A flat-faced round punch pressed 500 mg powder blend in a stainless-steel die with 0.5 in. inner diameter to form tablets. Sticking or ejection issues were not observed with the formulation in Table 3. Alcohol wipes were used to clean both die and punch before and after each compression. Once the tablet was made, it was tested by the Texture Analyzer (Texture Technologies Corp., USA) to measure the breaking force of tablets under the diametrical compression test. During breaking force measurement, each tablet was placed vertically on the plate, and a flat punch was applied gradually down to break the tablet. The breaking force was automatically recorded. Eq. (1) (Fell and Newton, 1970) was applied to calculate the tensile strength for each formulation and compaction force. In the equation, σ is tensile strength, F is the tablet breaking force, D_t is the tablet diameter, and t is the thickness of the tablet. Each pressure was replicated 5 times, and all of

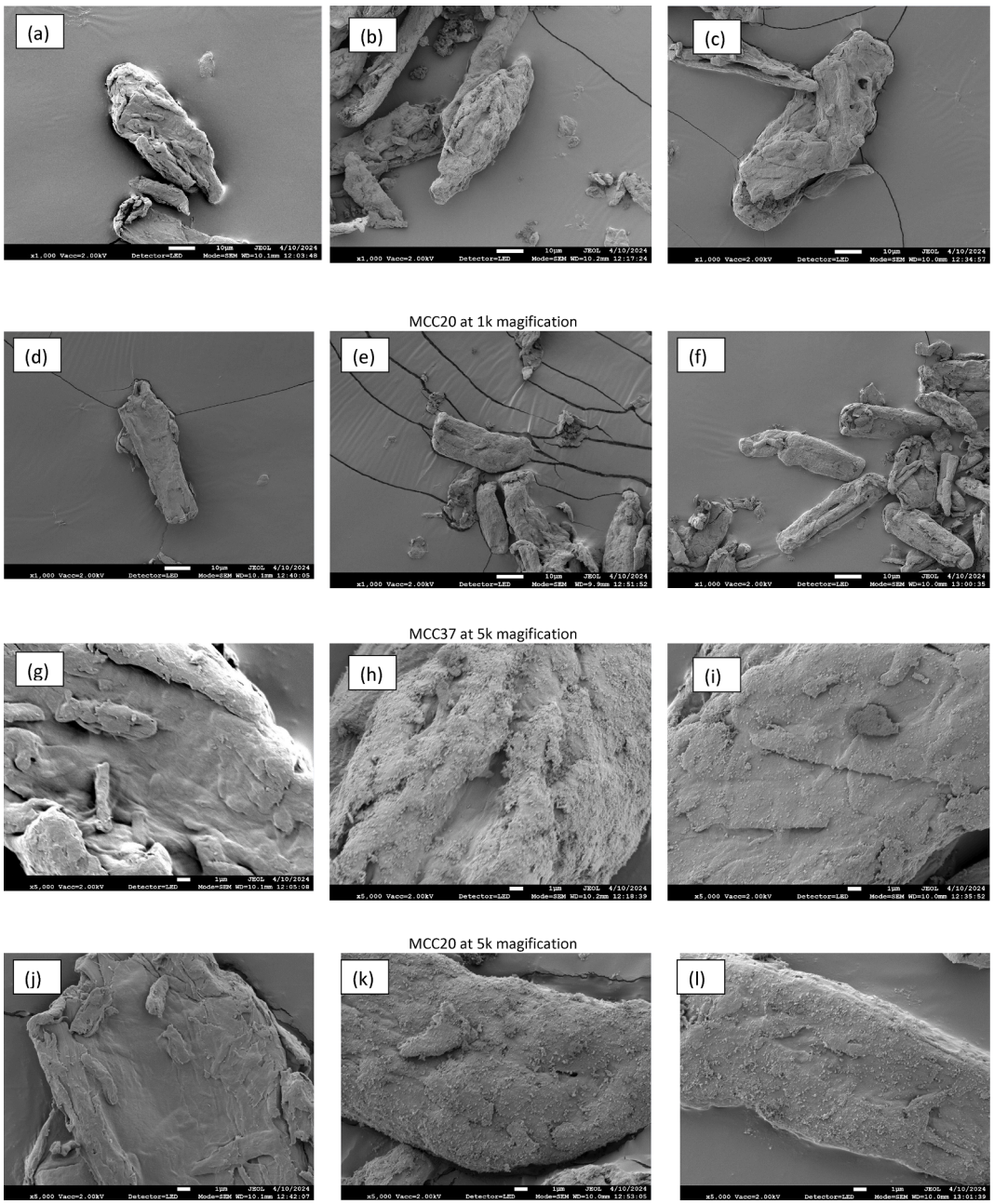

Fig. 1. SEM images of (a) uncoated MCC37, (b) MCC37 coated with 1 wt% A200, (c) MCC37 coated with 115 %SAC A200, (d) uncoated MCC20, (e) MCC20 coated with 1 wt% A200, (f) MCC20 coated with 115 %SAC A200ely at 1 k magnification; (g) uncoated MCC37, (h) MCC37 coated with 1 wt% A200, (i) MCC37 coated with 115 %SAC A200, (j) uncoated MCC20, (k) MCC20 coated with 1 wt% A200, and (l) MCC20 coated with 115 %SAC A200 at 5 k magnification.

the tablets broke in a tensile manner.

$$\sigma = \frac{2F}{\pi D_t t} \quad (1)$$

2.5. Particle sizing via laser diffraction

D10, D50, D90 and D3,2 was measured by utilizing Sympatec Helos/Rodos laser diffraction particle size analyzer (Sympatec Inc., NJ) at the dispersion pressure of 1.0 bar. This dispersion pressure resulted in the most consistent particle size distribution measurements as other studies prove (Huang et al., 2017; Kunnath et al., 2018). D3,2 measured by Helos/Rodos laser diffraction particle size analyzer was employed to calculate surface area coverage (SAC). D50 is used to represent particle size in whole paper, except calculation of surface area coverage with D3,2.

2.6. Surface area coverage calculation

The Surface Area Coverage (SAC) is the theoretical proportion of the host particle's surface area covered by guest particles (Huang et al., 2017). It is emphasized that the SAC is meant only as a normalized measure of silica amount and does not convey actual SAC that may be attained; nor is it necessary that the actual SAC and theoretical SAC values are the same. Several factors, such as the quantity and type of silica employed and the surface area of the host particle, impact SAC. The theoretical SAC can be calculated using the subsequent equation, where D signifies the diameter of the host particle, d indicates the particle size of the guest particle, ρ_d and ρ_D are the material true densities of the guest and host particles (Kunnath et al., 2021), respectively, and Gwt

Table 3
Details of binary blend formulation.

Excipient (40 wt%)	API (60 wt%)
MCC37	mAPAP
MCC37	cAPAP
MCC37	IBU
MCC30	mAPAP
MCC30	cAPAP
MCC30	IBU
MCC25	mAPAP
MCC25	cAPAP
MCC25	IBU
MCC20	cAPAP
MCC37 + 1 wt%A200	mAPAP
MCC37 + 1 wt%A200	cAPAP
MCC37 + 1 wt%A200	IBU
MCC37 + 0.67 wt%A200	cAPAP
MCC37 + 0.43 wt%A200 (MCC37 + 115 %SAC A200)	cAPAP
MCC37 + 0.4 wt%A200	cAPAP
MCC30 + 1 wt%A200	mAPAP
MCC30 + 1 wt%A200	cAPAP
MCC30 + 1 wt%A200	IBU
MCC25 + 1 wt%A200	mAPAP
MCC25 + 1 wt%A200	cAPAP
MCC25 + 1 wt%A200	IBU
MCC20 + 1 wt%A200	cAPAP
MCC30 + 115 %SAC A200	cAPAP
MCC20 + 115 %SAC A200	cAPAP

% denotes the weight percentage of the guest particle relative to the host particle.

$$SAC = Gwt\% * \frac{D\rho_D}{4d\rho_d} * 100\% \quad (2)$$

2.7. Particle true density analysis

The true density of powder was determined using a Pycnometer (NOVA 3200, Quantachrome Instruments, Boynton Beach, FL, USA) with Helium gas. This experiment was conducted five times, and the average values are presented.

2.8. SEM

A Field Emission Scanning Electron Microscope (SEM) model EM JSM-7900F from JEOL USA was used. Samples were prepared by sputter-coated using an Au/Pt coating technique (Q150T 16017, Quorum Technologies Ltd, Laughton, East Sussex, England) to enhance conductivity during SEM imaging.

3. Results and Discussion

3.1. Effect of Dry Coating Different Fine Sized Excipients on Blends with Three Types of APIs

3.1.1. Blend flowability and bulk density Enhancements: Cohesive API type and excipient size at fixed 1 wt% A200 silica

First, the effect of dry coating of various sized MCC excipients were investigated for three different APIs, ranging in their primary particle sizes. Here, the type and amount of silica is fixed to better understand the effect of the excipient sizes, keeping in mind previous work that only examined one fine excipient size (Chen et al., 2019b). For reference, the flowability and bulk density of the three as-received model APIs, mAPAP, cAPAP, and IBU50, were measured, presented in Fig. 2a and Fig. 2b, respectively. Fig. 2a shows that these three APIs belong to distinctly different flow regimes and correspondingly, Fig. 2b indicates that the bulk density of mAPAP is much lower than cAPAP and IBU50. The poor flowability values for all three APIs and relatively low bulk density values signify potential challenges in formulating them at high drug loading for successful tableting without requiring dry or wet granulation (Chen et al., 2019b).

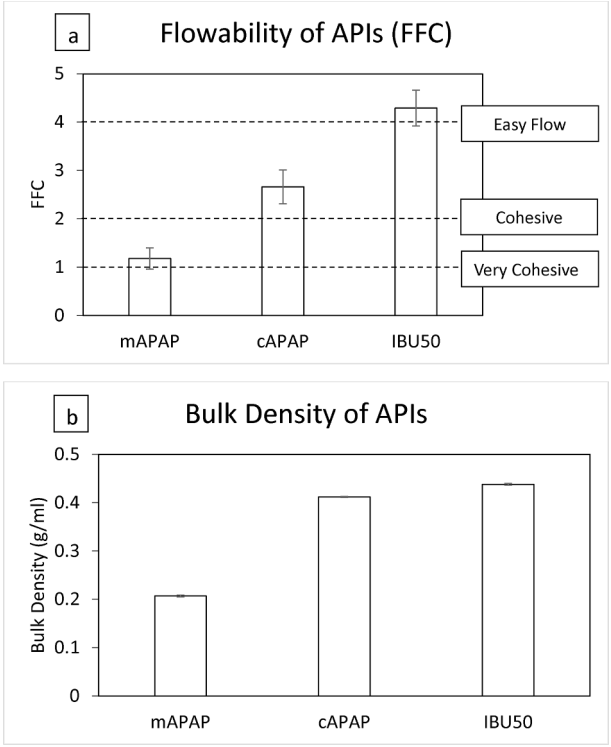

Fig. 2. Flowability (a) and bulk density (b) of as received mAPAP, cAPAP, and IBU50. Note that the bulk density error bars are very small due to excellent repeatability of the measurements.

The particle sizes of both coated and uncoated MCCs, milled at different sizes, with or without silica coating, are detailed in Table 2. Excipients of different sizes were deliberately chosen to learn how excipient size, along with dry coating, can influence bulk powder properties as related to the API size. A200 silica was chosen based on its reported superior tablet tensile strength compared to silica Aerosil R972P, albeit slightly lesser performance for enhanced flowability, both are attributed to A200 silica's higher surface energy (Chen et al., 2018b). Blends were formulated at a 60 wt% drug loading, a challenging level to achieve optimal bulk density, flowability, and tensile strength for these APIs known to have poor flowability, bulk density and compactability on their own. The flowability and bulk density of uncoated and 1 wt% A200-coated MCC excipients by themselves were found to follow similar trends as previously reported, see Table S1, supplementary material (Chen et al., 2018a; Chen et al., 2018b).

The flowability and bulk density (BD) of these three APIs at 60 wt% loading with three sizes of MCC, 25 μm, 30 μm, and 37 μm, are presented in Fig. 3 in form of phase maps, which are effective for conveying changes in key properties of blends. Likewise, the results for their tensile strength are presented by plotting FFC versus tensile strength in the next sub-section. Fig. 3 also includes the FFC vs. bulk density for Prosolv® 50 blends, presented for reference from previous work, indicated using red markers (Chen et al., 2019b). For reference, the D50 size of Prosolv® 50 is 65 μm. The results indicate that, in the absence of dry coating, various fine-grade excipients do not significantly enhance the FFC of mAPAP and cAPAP blends, mainly because these two APIs are very cohesive or cohesive and the uncoated excipients are not expected to be well flowing due to their fine sizes. Even for the largest sized and least cohesive API of three, i.e., IBU, the FFC of its blend with MCC37, the largest sized excipient, did not attain much improved free-flowing characteristics, although it achieved the highest FFC amongst all the IBU blends. Although for cAPAP, Prosolv® 50 blends did slightly better as compared

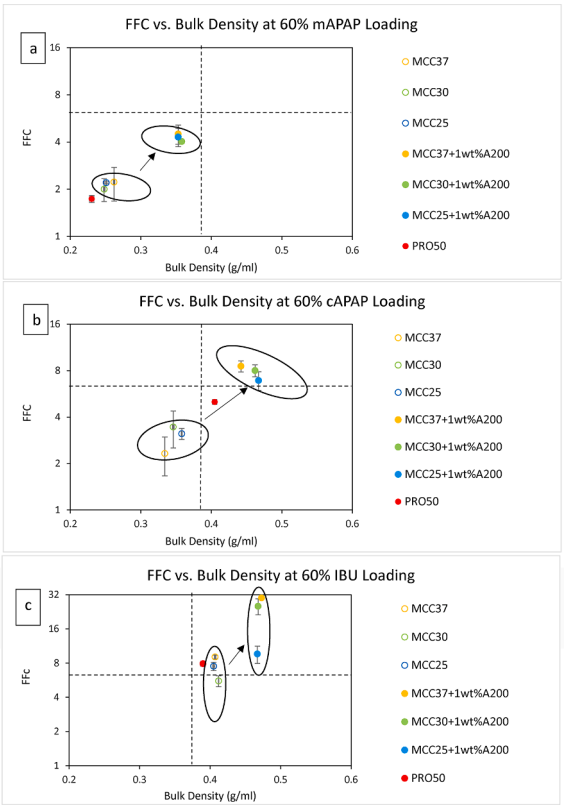

Fig. 3. FFC versus bulk density maps of binary blends of a) mAPAP, b) cAPAP, and c) IBU at 60 wt% drug loading with uncoated MCC37, MCC30, and MCC25, and dry coated MCC37, MCC30, and MCC25 with 1 wt% A200 as well as uncoated 20 μm Avicel 105 and coated 20 μm Avicel 105 with 1 wt% A200. The vertical dashed line represents bulk density criteria for direct compression (0.38 g/ml) and the horizontal dashed line represents the FFC criteria for direct compression (6.8). The markers with red color represent Prosolv 50® results in each figure, adopted from (Chen et al., 2019). Ellipses drawn in each figure points to the groups of uncoated materials and coated materials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Particle size and FFC of APIs used in binary blend formulation.

APIs	D10 (μm)	D50 (μm)	D90 (μm)	FFC
mAPAP	2	7	25	1.18
cAPAP	4	23	87	2.66
IBU	9	53	101	4.29

to the uncoated milled MCC blends, they performed worse for mAPAP and IBU. This was surprising and counterintuitive. In contrast, following dry coating, the FFC of all fine API blends showed a substantial improvement, likely due to the presence of the silica on particle surfaces leading to reduced particle adhesion force (Chen et al., 2008). With dry coating of fine MCCs, the FFC of 3 uncoated IBU blends was above 10 (Fig. 3c), the FFC of 3 uncoated mAPAP blends increased from an average of 2.14 to an average of 4.28 (Fig. 3a), and 3 uncoated cAPAP blends increased from an average of 2.96 to an average of 7.82 (Fig. 3b). On one hand, the FFC improvement for mAPAP (7.3 μm) was much smaller than either cAPAP (23.3 μm) or IBU (53 μm) since mAPAP has a much smaller particle size and higher adhesion force (particle size refers to Table 4) (Chen et al., 2008). On the other hand, the extent of enhancement in terms of flow category for mAPAP was nearly the same as for IBU; namely, both cases achieving about one flow category uptick. Most interestingly, cAPAP blends attained almost two flow category enhancements; moving up from nearly cohesive to nearly flow flowing.

Remarkably, cAPAP and IBU blends with dry coated MCCs attained adequate flowability enhancements, even in some cases reaching free-flow category, while mAPAP blends nearly attained the easy-flow category even though mAPAP was very cohesive. The outcomes for the blends with mAPAP were harder to differentiate in terms of the effect of different sized dry coated excipients, likely due to the finest API size and high drug loading, leading to the blend properties being dominated by very cohesive constituent (Chen et al., 2019b; Kunnath et al., 2021; Kunnath et al., 2023). For cAPAP, the blend FFC values were somewhat influenced by the excipient size, MCC25 blends having an FFC of under 7 yet > 6.8, whereas MCC37 blends attained FFC of over 8.5. Similar trend was observed for IBU blends where MCC25 being the least effective, yet FFC of nearly 10, while MCC30 and MCC37 blends attained free-flow categories of FFC well over 10 each. The performance of Prosolv® 50 blends with cAPAP and IBU remained rather poor and did not follow the trend of milled and dry coated MCCs enhancements, indicating that excipient size alone may not dictate blend performance. In summary, the effect of the size of dry coated fine excipients was more evident as the API size increased, and the blend FFC enhancements were more significant for the blends with two larger sized APIs, cAPAP and IBU.

The bulk density (BD) outcomes depicted in Fig. 3 indicate significant improvements for dry coated milled MCC excipients, as compared with uncoated milled MCCs for all three APIs. For mAPAP, the uncoated milled MCC blends attained BD of about 0.25 g/ml, which would be expected considering its high drug load and its BD being low, about 0.2 g/ml. It is noted that the BD for uncoated MCCs was also expected to be low, about 0.34 g/ml, see for reference (Chen et al., 2018a). For dry coated MCCs, the BD increased to over 0.35 g/ml, representing a significant increase of about 40 %, and essentially reaching DC capable level. For cAPAP and IBU, since their sizes are larger, the average increase in BD was a little less, about 30 % and 18 %, respectively, although all blends with dry coated milled MCCs reached direct compression capability. Overall, regardless of the coating on milled MCCs, only minor differences between various excipient sizes were observed, particularly for mAPAP and IBU. This difference in bulk density for the cAPAP blends could potentially be explained by the size ratio of excipient and API (Huang et al., 2017; Kunnath et al., 2018) since the size of cAPAP is comparable to all milled MCC excipients. When comparing coated and uncoated blends, the bulk density appeared to be influenced solely by whether the excipient was coated or not, indicating less sensitivity to excipient size, as long as the excipient size was significantly larger or smaller than the API size.

The bulk density values of the blends of three APIs with Prosolv® 50 were rather low in comparison to the levels attained using any of three sized dry coated milled MCCs. In fact, they failed to outperform even uncoated milled MCC blends for mAPAP and IBU, although the BD values for cAPAP blends were reasonably good even though not as good as those for dry coated milled MCCs.

In summary, one may conclude that dry coated milled MCC led to significant enhancements in both the FFC and BD, as illustrated by three arrows pointing from the uncoated group of blends to dry coated group of blends in three plots of Fig. 3. As for the effect of the varying fine sizes of MCC excipients, the size effect was less pronounced, yet noticeable except for the finest API, mAPAP. The largest sized excipient, MCC37, attained the most improvements in FFC. The reason for this could be in part due to the relatively close sizes of the API and excipients for cAPAP and IBU, and in part due to the available silica on the surface of excipient that could potentially transfer to the API during blending, leading to enhanced flowability of the blend. The detailed discussion of silica transfer and related synergy has been presented in previous papers that have alluded to such possibilities (Chen et al., 2019b; Kim et al., 2023; Lin et al., 2024). As excepted, similar situation is present here, as confirmed by the SEM images, see Fig. S1, in the supplementary material. As shown in those SEM images, for the blends that contained silica coated MCCs, the presence of silica on the API surface is evident.

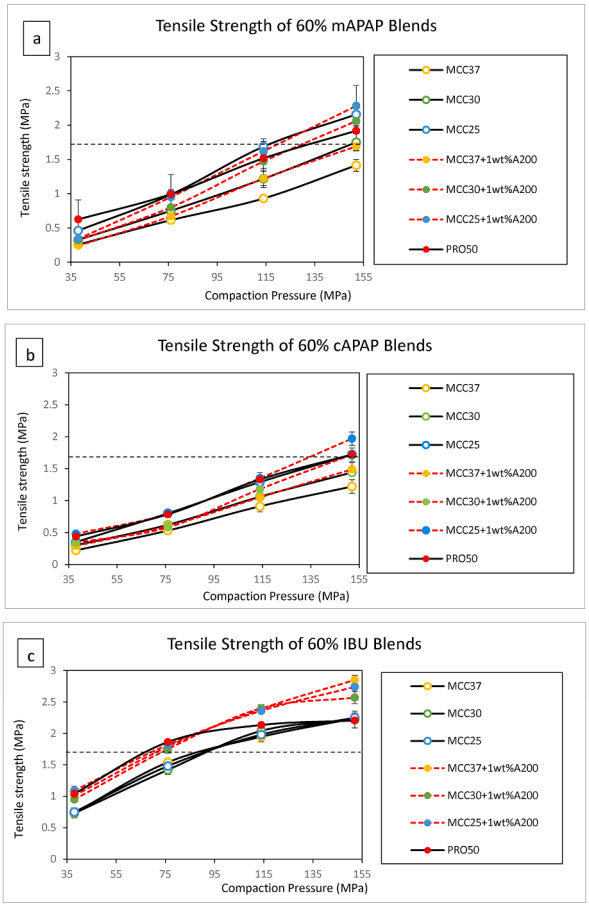

Fig. 4. Tabletability curves of a) mAPAP, b) cAPAP, and c) IBU with three sizes of MCC37, MCC30, and MCC25 and dry coated MCC37, MCC30, and MCC25 with 1 wt% A200 as well as uncoated 20 μm Avicel 105 and coated 20 μm Avicel 105 with 1 wt% A200. The amount of excipient and API in the formulation are 40 wt% and 60 wt%, respectively. The markers with red color represent Prosolv 50® results in each figure, (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
adopted from (Chen et al., 2019). The horizontal dashed line represents the desirable minimum tablet tensile strength of 1.7 MPa (Pitt and Heasley, 2013).

Whereas such silica presence is not evident for the blends that did not contain silica coated MCCs. The availability of silica on MCC surfaces may have led to its transfer to the uncoated API surfaces and helped enhance the blend flowability to appreciable levels. That may also in part explain why Prosolv® 50 blends, particularly for IBU despite the very closely matched size, did not attain very good flowability enhancements because even though Prosolv® 50 includes nearly double the amount of silica, most of that may be contained within the particles and not available on the surface for easy transfer to other blend ingredients (Rojas and Kumar, 2012).

3.1.2. *Compaction Properties: The effect of API type and excipient size*

The mechanical properties of tablets, such as the tensile strength (TS) calculated using Equation (1), are expected to be influenced by many factors including API type and excipient size and investigated here for three APIs. Tableting was performed for all blends presented in Fig. 2 and Table 3. The results are shown in Fig. 4 for the tensile strength of tablets of mAPAP, cAPAP and IBU, made using the binary blends with uncoated and coated MCC25, MCC30, and MCC37, at 4 compression pressures for each case. In addition, the results for Prosolv® 50, adopted from (Chen et al., 2019b) are also shown in Fig. 4 for the sake of comparison. The tensile strength curves for the tablets with uncoated excipients are shown with a solid line, while those with dry coated excipients are shown by a dashed line. For uncoated milled MCC, their mAPAP and cAPAP blends exhibit the expected trends of higher TS as the excipient size decreased and/or the compression pressure increased, Fig. 3a and 3b. Remarkably, the tablet TS improved appreciably for dry coated MCC37 and MCC30 blends with mAPAP and cAPAP, Fig. 3a and 3b, while the difference between uncoated and dry coated MCC25 blends was less. For IBU, the largest of three APIs, the impact of uncoated milled excipient size on tablet TS was minimal, Fig. 4c. It is likely that the size effect of excipient is lessened by high drug loading of 60 wt % for IBU, which is known to have much lower bonding strength in comparison to MCC (Chen et al., 2018a; Chen et al., 2019b). In contrast, all three milled and coated MCC excipients exhibited appreciable increase in tablet TS for IBU blends.

Overall, for all three APIs, one or more milled and coated MCCs could achieve the tablet TS values of 1.7, which is considered as the minimum desirable value (Pitt and Heasley, 2013) shown as a horizontal dashed line, or higher. For mAPAP, all three milled coated MCCs could attain that mark at the highest compression pressure, whereas for IBU, it occurred even for the lower compression pressure of 76 MPa. Interestingly, cAPAP tablets attained such level of TS for the two finer sized dry coated MCCs, but not for the largest sized. Overall, it is evident that dry coating of fine excipients led to positive impact on TS, which was generally related to the sizes of the API and excipients. Finer APIs benefitted more from finer excipients, especially at higher compression pressures. Such improvements are generally in line with the previous work where one of the constituents was dry coated (Chen et al., 2019b; Huang et al., 2015b). It is hypothesized that the reduced particle cohesion force resulting from dry coating may improve particle rearrangement during tableting, leading to slight improvement despite anticipated loss in bonding strength due to A200 silica coating (Balakrishnan et al., 2010; Garr and Rubinstein, 1991; Huang et al., 2015b; Kunnath et al., 2018). The hypothetical particle rearrangement facilitated due to dry coating is expected to be more crucial at high compression pressure, because tablets are less porous, please see Fig. S2, supplementary material, and the resistance to particle rearrangement during compaction without the presence of silica may be more difficult.

Tablet compaction results shown in Fig. 4 include the data for Prosolv® 50 blends with mAPAP, cAPAP and IBU, adopted from (Chen et al., 2019b). Performance of Prosolv® 50 blends for mAPAP and cAPAP was adequate only at the highest compaction pressure. In contrast, dry coated MCC25 and MCC30 blends achieved higher TS values for these two APIs. Rather interestingly, Prosolv® 50 blends with the largest API, IBU, reached compression saturation at two higher compression levels, and plateaued at a value of about 2 MPa. In summary, the results for the blends prepared using dry coated milled MCCs demonstrated suitability for such fine, surface modified excipients for enhancing DC processability for high drug loaded blends of fine APIs. The particle size of these excipients played an important role; finer excipients being better for attaining higher tensile strengths, while coarser excipients being more advantageous for enhanced flowability, particularly for the two finer APIs. Exemplary properties attained by these blends were only attained by the dry coated versions of the milled MCC-based fine excipients.

3.2. *Effect of dry coating – Varying silica amount*

3.2.1. *Flowability and bulk Density: A case study with varying silica amounts*

The findings presented in Section 3.1 revealed notable enhancements in flowability, bulk density, and tablet tensile strength through the utilization of dry coated fine MCC-based excipients. Such improvements were particularly prominent in blends containing two of the comparatively larger sized APIs, cAPAP and IBU, as depicted in Fig. 5. In these blends, the tablet formulations nearly achieved or successfully attained DB-DC capability. For the finest API, mAPAP, although the FFC, BD, and

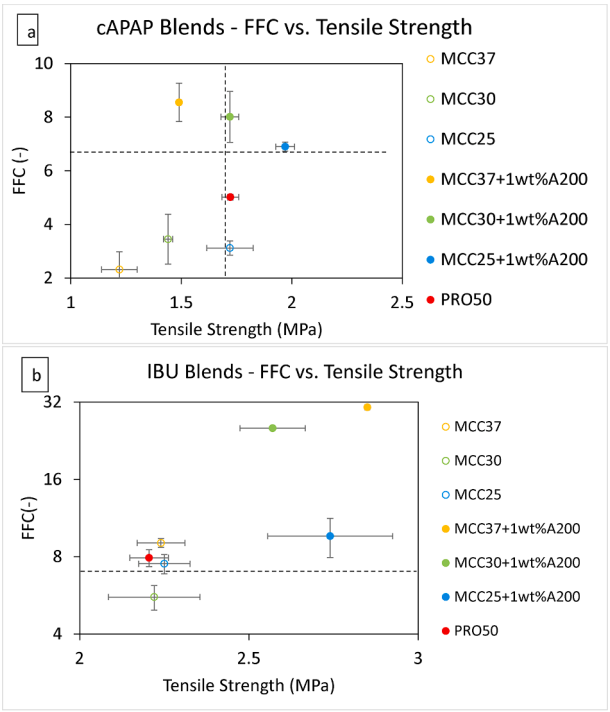

Fig. 5. Flowability and tablet tensile strength phase map for tablets compressed at 152 MPa for 60 wt% cAPAP (a) with three sizes of dry coated milled MCCs; i.e., MCC37, MCC30, and MCC25, and, IBU (b) with three sizes of dry coated milled MCCs; i.e., MCC37, MCC30, and MCC20, blends with two silica amounts: 1 wt% A200 (corresponding to %SAC reported in the last column of Table 2) and 115 %SAC A200. The marker with red color in each plot represents Prosolv 50® results, adopted from (Chen et al., 2019). The horizontal dashed line represents the FFC criteria for direct compression (FFC = 6.8). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

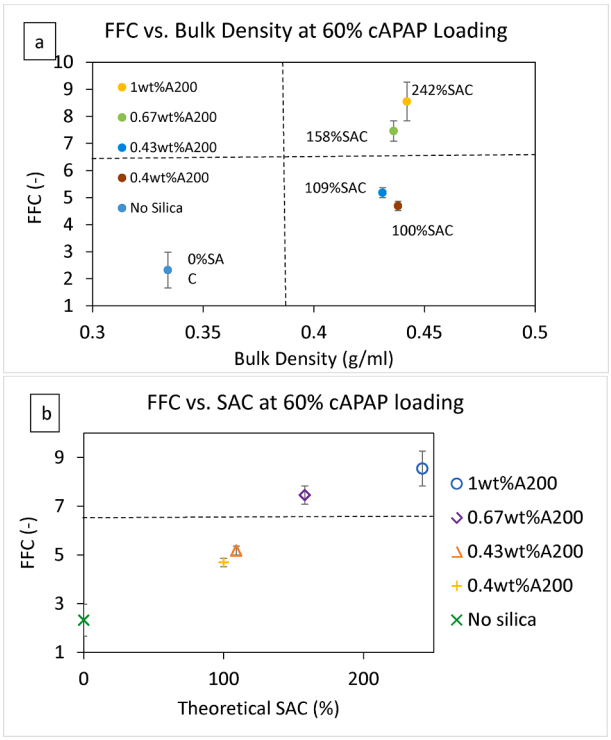

Fig. 6. (a) FFC versus bulk density maps and (b) FFC versus SAC maps of 60 wt % cAPAP blends with 40 wt% dry coated MCC37 with four silica amounts: 0.4, 0.43, 0.67, and 1 wt% A200.The vertical dashed line represents bulk density criteria for direct compression (0.38 g/ml) and the horizontal dashed line represents the FFC criteria for direct compression (6.8). No silica refers to blend without dry coating. Note: The error bars of bulk density have been provided but are too small to be easily visualized.

TS enhancements were significant, see Figs. 2 and 3, direct compaction (DC) capability was not attained. For cAPAP, Fig. 5a, the flowability of its blends with dry coated MCCs reached adequate levels for DC capability. However, only the blends with two finest dry coated excipients (MCC25 and MCC30) attained an adequate TS level of 1.7 MPa. For IBU, Fig. 5b, not only the flowability and bulk density of its blends with dry coated MCCs reached adequate levels for DC capability, but also all the blends with the dry coated excipients attained excellent TS values, well above the 1.7 MPa. Notably, the cAPAP blend with Prosolv® 50 failed to attain DC capability or adequate tablet TS, while its blend with IBU was significantly outperformed by all three milled and dry coated MCC blends.

A question, which warrants further investigation, may be asked if the amount of coated silica may be adjusted to achieve a compromise between the enhanced flowability and tablet strength so that even better outcomes could be obtained. Noting that usually more silica, better the flowability, but poorer the tablet strength. That question is considered next, where the silica amount was reduced based on either the wt % or based on a normalized measure such as theoretical surface area coverage (SAC). It is noted that the same amount of silica will lead to different SAC values according to the milled excipient sizes (Chen et al., 2018a). For a fixed wt %, finer excipient would have a lower SAC value as compared to a coarser excipient. The SAC could be estimated by Eq. (2) (Chen et al., 2018a; Chen et al., 2018b; Chen et al., 2019b; Chen et al., 2008). In the first part of this investigation, a fixed excipient size of 37 μm was considered for four different silica amounts to be mixed with the medium sized API, cAPAP. Towards that goal, MCC101 was pre-blended with various silica loadings with an intent to achieve various SAC levels, shown in Table 2, and then milled to 37 μm; followed by blending with 60 wt% cAPAP. Thus, MCC101 was milled and coated with 1 wt% A200, 0.67 wt% A200, 0.43 wt% A200, or 0.4 wt% A200, leading to intended SAC levels of 241 %, 158 %, 109 %, or 100 %, respectively for the resulting dry coated MCC37. Normalized silica amount as SAC% strictly represents the theoretical percentage of the particle surface area that is covered by silica. When the SAC% is higher than 100 %, it implies that silica would not be mono-layered and may be present as small aggregates. The flowability and bulk density for these blends were measured, shown in Fig. 6a and 6b. For control, the results for uncoated MCC37 blends are also presented. The FFC of 1 wt% A200 silica coated MCC37 blend with 60 wt% cAPAP is higher than 8 but reduced amount of silica led to reduced flowability enhancement, yet, attaining FFC of well above 4 at the lowest amount of silica. Note that the FFC of uncoated MCC37 blends with cAPAP is only 2.32 and the bulk density is also rather low, 0.334 g/ml. Thus, the impact of even the lowest level of silica coating of MCC37 on FFC was significant as it reached a value of 4.7, hence easy flow category. The relationship between FFC and the amount of silica exhibited a significant trend, with values rising to 5.2, 7.6, and 8.6 at silica concentrations of 0.43 wt%, 0.67 wt%, and 1.0 wt%, respectively. Although the influence of silica amount on bulk density was less significant, the presence of silica in the blend proved to be crucial. There was clear bulk density improvement observed for the cases where the silica is included. The improvement resulted by silica coating appear to agree with previous work, although that work only examined individual MCCs of different sizes and not their blends (Chen et al., 2018a). These results show that for a fixed excipient size, increasing dry coated silica amount could be considered for enhanced blend flowability, although increased silica amount could have a negative impact on the blend compaction, which is examined in the next sub-section for the same cases.

Next, 60 wt% cAPAP blends with three different sized milled and

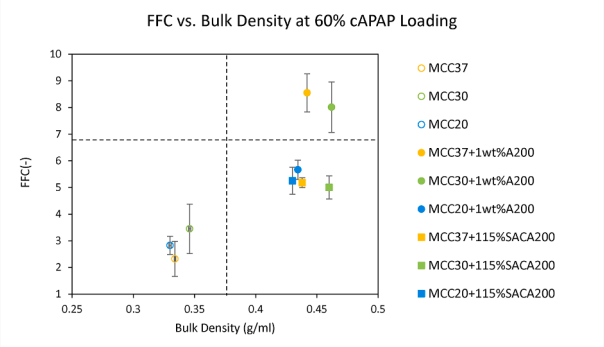

Fig. 7. FFC versus bulk density maps of 60 wt% cAPAP and milled MCC blends of three differing milled MCC sizes, 37, 30, and 20 μm, and three different MCC coating amounts: uncoated, dry coated 1 wt% A200, and dry coated 115 %SAC A200. Note that 1 wt% A200 silica corresponds with a theoretical SAC of 241 %, 205 %, and 141 %, for MCC37, MCC30, and MCC20, respectively. The vertical dashed line represents bulk density criteria for direct compression (0.38 g/ml) and the horizontal dashed line represents the FFC criteria for direct compression (6.8).

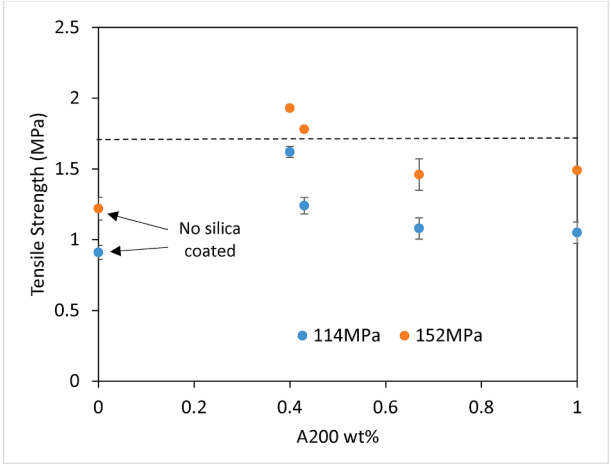

Fig. 8. Tablet tensile strength at two compaction pressures, 114 and 152 MPa, of 60 wt% cAPAP and dry coated MCC37 blends with four silica amounts: 0.4, 0.43, 0.67, and 1 wt% A200. The horizontal dashed line represents the desirable minimum tablet tensile strength of 1.7 MPa (Pitt and Heasley, 2013).

coated excipients were considered to further investigate the effect of silica amount on bulk density and flowability. Towards that purpose, fixed silica SAC value of 115 %, which was slightly higher than ideal 100 %, was selected to assure enough silica was available to achieve good actual coverage. Due to difficulty in precisely controlling the achieved SAC exactly at 115 % SAC, the calculated SAC around 115 ± 6 % are labelled as 115 %SAC.These three sizes were about 37 μm, 30 μm, and 20 μm, labelled MCC37, MCC30, and MCC20. When coated with 1 wt% A200, those excipients attained a theoretical SAC of 241 %, 205 %, and 141 %, respectively. The results for corresponding 60 wt% cAPAP blends are shown in Fig. 6 along with 1 wt% silica coated excipient blends. The silica amounts and corresponding SACs of dry coated materials used in Fig. 7 may also be found in Table 1. The results for FFC and bulk density plotted in Fig. 7 were generally consistent with the results shown in Fig. 6a with respect to the impact of silica amount. However, two striking trends could be observed. First, for fixed silica SAC of 115 %, the excipient size did not have a significant impact on the FFC of the blends. Nonetheless, those values were remarkably higher as compared with the uncoated MCC blends. FFC increased from an averaged value of about 3 to well over 5, hence at least one flow category improvement. However, these FFC values fell somewhat short of what has been recommended as a DC capability (Chen et al., 2019b). The bulk density values increased from an averaged value of about 0.33 g/ml to over 0.43 g/ml for MCC 20 and MCC37 blends, an increase of over 30 %. Interestingly, the MCC30 blends reached the highest bulk density of 0.46 g/ml. For the fixed higher concentration of 1 wt% silica, which corresponded to significantly higher theoretical SAC values compared to 115 % SAC, blends incorporating coated milled MCCs demonstrated greater enhancements in flowability and bulk density. Moreover, the influence of MCC size was noticeable for the 1 wt% silica coating although MCC20 1 %A200 and MCC20 115 % SAC exhibited overlapping error bars for FFC due to their almost similar SAC (corresponding SAC are shown in Table 2). The blends with only the two larger sized excipients, MCC30 and MCC37, attained DC capability.

3.2.2. *Compaction Properties: A case study with varying silica amounts*

In general, dry coating has proven to be an effective method for enhancing the bulk density, flowability, and tensile strength of binary blends. Overall, whereas higher silica amounts are expected to enhance flowability, lower silica amounts are likely to yield higher tablet tensile strength. Therefore, the blends discussed in the previous section were considered here for tablet compaction studies.

First, the tensile strength blends with various silicified MCC37 with silica amounts varying from 0.4 wt% to 1.0 wt% are shown in Fig. 8. The tensile strength increased for the two blends with lower silica amount coating; most likely less silica implied higher surface energy of the MCC powders, thus stronger bonding strength (Chen et al., 2018b; El Gindy and Samaha, 1982)). Interestingly, the tensile strength at both 0.67 wt% and 1 wt% were similar, suggesting that as the silica amount increased, the decrease in tensile strength may have leveled off. That trend could be attributed to silica agglomeration (Fig. 1h), likely to occur at high SAC due to the excessive silica (Zheng et al., 2020), and might have also hindered the reduction in surface energy resulting from silica coating (Huang et al., 2015a).

Next, the tensile strength of 60 wt% cAPAP with the 1 wt% and 115 %SAC dry coated MCC blends at two compression pressures, 114 and 152 MPa, were evaluated to assess the tensile strength loss encountered from silica coating, shown in Fig. 9. In all these results for both 1 wt% and 115 %SAC dry coated blends, the tensile strength increased as the excipient size decreased, and compression force increased. More importantly, the blends with lesser silica amounts, represented by 115 % SAC dry coated blends, led to higher tensile strength and reached level above 1.7 MPa for all three excipients at the 152 MPa compression pressure. Here, too, less silica meant higher surface energy of the coated excipients, thus stronger bonding strength (Chen et al., 2018b; El Gindy and Samaha, 1982). Interestingly, MCC20 shows decreased tensile strength with 1 wt% A200 coating but slightly improved tensile strength with 115 % SAC coating. This phenomenon indicated that finer sized MCC was more sensitive to silica coating and silica amount, which could lead to decreased MCC bonding strength. These results convey that the combined effect of the excipient size and silica amount might offer practitioners with options to achieve desired levels of tablet tensile strength; for example, almost similar outcomes could be achieved for cAPAP blends with larger sized MCC37 with lesser silica of 115 %SAC A200 or finer sized MCC30 with 1 wt% A200.

The compaction results, combined with those for the flowability from the previous section are presented next in Fig. 10 to better visualize the interplay of excipient size and silica amounts for the medium sized API, cAPAP. For example, as the excipient size increased, except for MCC37, cAPAP blends with MCCs coated with the higher amount of silica (1 wt%), see the solid blue trend line/arrow (for better visualization), exhibited better flowability while maintaining good tensile strength (compressed at 152 MPa). Conversely, as the excipient size increased, the cAPAP blends with MCCs coated with the lower amount of silica (115 %SAC), see the dashed blue trend line/arrow, the flowability remained constant at slightly below the desired FCC for DC capability, while the tensile strength gradually reduced yet achieving

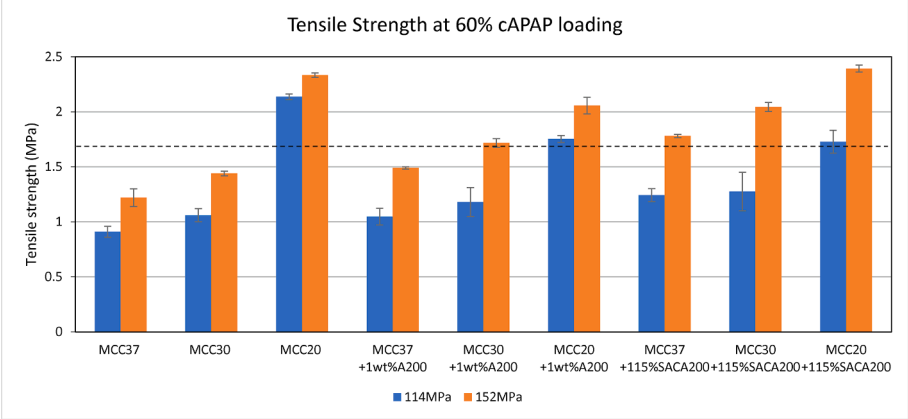

Fig. 9. Tablet tensile strength at two compaction pressures, 114 MPa and 152 MPa, for 60 wt% cAPAP and three sizes of dry coated milled MCC37, MCC30, and MCC20, blends with two silica amounts: 1 wt% A200 (corresponding to %SAC reported in last column of Table 2) and 115 %SAC A200. The results for no silica coated MCC blends are also presented; denoted by MCC37, MCC30, and MCC20. The horizontal dashed line represents the desirable minimum tablet tensile strength of 1.7 MPa (Pitt and Heasley, 2013).

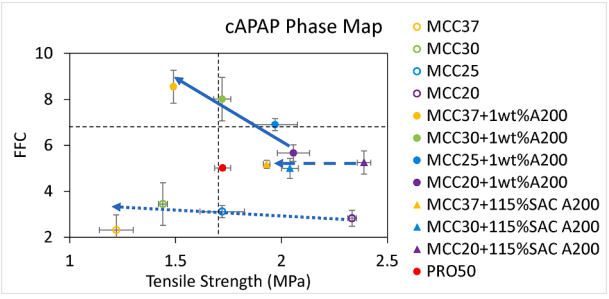

Fig. 10. Flowability and tablet tensile strength phase map at 152 MPa of 60 wt % cAPAP and three sizes of dry coated milled MCC37, MCC30, and MCC20, blends with two silica amounts: 1 wt% A200 (corresponding to %SAC reported in last column of Table 2) and 115 %SAC A200. The marker with red color represents Prosolv 50® results, adopted from (Chen et al., 2019). The horizontal dashed line represents the FFC criteria for direct compression (6.8) and the vertical dashed line represents the desirable minimum tablet tensile strength of 1.7 MPa (Pitt and Heasley, 2013). Three different arrows depict the effect of the increasing excipient size on TS and FFC; dotted arrow for uncoated, dashed arrow for 115 %SAC coated, and solid arrow for the highest silica amount of 1 wt% for the milled fine excipients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the desired TS level. On a side note, as the excipient size increased from 20 μm to 30 μm, the cAPAP blends with uncoated milled MCCs had slightly increased FFC values, see the dotted blue trend line/arrow. Clearly, MCC37 remains an exception to that trend. Similar trends were observed for mAPAP and IBU blends with 1 wt% A200 coated MCCs, see Fig. S3 and Fig. 5(b), respectively. Note that IBU blends achieved high FFC and TS levels, but mAPAP blends did not reach the desired FFC level. Overall, the trends shown in this figure demonstrate that the size and silica amount for fine milled MCC-based excipients provide the flexibility in developing DC capable, high drug load, fine API formulations. Interestingly, this figure demonstrated that cAPAP blend with Prosolv® 50 could not reach the required FFC level, suggesting major differences in the behavior of silicified excipients from the milled and dry coated fine excipients for high drug loaded blends of fine APIs.

4. Conclusions

Milled and dry coated fine grade MCC-based excipients were found to greatly enhance flowability and bulk density of high drug loaded binary blends of all three fine APIs, mAPAP, cAPAP, and IBU, as compared to their blends with the uncoated fine excipients, or their blends with a commercially available silicified excipient such as Prosolv® 50. Remarkably, there was no negative impact on the tablet tensile strength for any of those blends, which is contradictory to the expectation of reduced TS because of the presence of lower surface energy material like silica. Instead, the tablets of all three APIs reached or exceeded the desired TS level above what was obtained for the corresponding blends with uncoated milled MCCs. As a major novel outcome, milled and silica coated fine MCCs could promote DB-DC tableting for fine cAPAP and not so fine IBU blends at 60 wt% loading by achieving adequate flowability as well as tensile strength, while achieving significant yet perhaps inadequate level of FFC for DB-DC processability of the fine mAPAP blends without having to dry coat the fine API itself. The results for the effect of the lesser silica amount indicated that it had a positive impact on tablet tensile strength, whereas the higher silica amount had a positive impact on blend flowability. Overall, finer silica coated excipients impart key desired attributes, flowability and tensile strength, to highly loaded fine API blends. In addition, the combined effects of the excipient size and silica amount could be considered to identify the best combination for achieving the desired levels of both the blend flowability and tablet tensile strength for high drug loaded blends of fine and cohesive APIs.

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CRediT authorship contribution statement

Zhixing Lin: Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bian Cabello:** Investigation. **Christopher Kossor:** Writing – review & editing, Visualization. **Rajesh Davé:** Writing – review & editing, Visualization, Supervision, Resources, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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References

Balakrishnan, A., Pizette, P., Martin, C., Joshi, S., Saha, B., 2010. Effect of particle size in aggregated and agglomerated ceramic powders. Acta Mater. 58, 802–812.
Chen, H., Aburub, A., Sun, C.C., 2019a. Direct compression tablet containing 99% active ingredient—a tale of spherical crystallization. J. Pharm. Sci. 108, 1396–1400.
Chen, L., Ding, X., He, Z., Fan, S., Kunnath, K.T., Zheng, K., Dave, R.N., 2018a. Surface engineered excipients: II. Simultaneous milling and dry coating for preparation of fine-grade microcrystalline cellulose with enhanced properties. Int. J. Pharm. 546, 125–136.
Chen, L., Ding, X., He, Z., Huang, Z., Kunnath, K.T., Zheng, K., Dave, R.N., 2018b. Surface engineered excipients: I. improved functional properties of fine grade microcrystalline cellulose. Int. J. Pharm. 536, 127–137.
Chen, L., He, Z., Kunnath, K.T., Fan, S., Wei, Y., Ding, X., Zheng, K., Dave, R.N., 2019b. Surface engineered excipients: III. Facilitating direct compaction tableting of binary blends containing fine cohesive poorly-compactable APIs. Int. J. Pharm. 557, 354–365.
Chen, Y., Yang, J., Dave, R.N., Pfeffer, R., 2008. Fluidization of coated group C powders. AIChE J 54, 104–121.
Doelker, E., Massuelle, D., Veuillez, F., Humbert-Droz, P., 1995. Morphological, packing, flow and tableting properties of new Avicel types. Drug Dev. Ind. Pharm. 21, 643–661.
El Gindy, N.A., Samaha, M.W., 1982. Tensile strength of some pharmaceutical compacts and their relation to surface free energy. Int. J. Pharm. 13, 35–46.
Fell, J., Newton, J., 1970. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 59, 688–691.
Freeman, R., 2007. Measuring the flow properties of consolidated, conditioned and aerated powders — A comparative study using a powder rheometer and a rotational shear cell. Powder Technol. 174, 25–33.
Garr, J., Rubinstein, M., 1991. The effect of rate of force application on the properties of microcrystalline cellulose and dibasic calcium phosphate mixtures. Int. J. Pharm. 73, 75–80.
Han, X., Ghoroi, C., To, D., Chen, Y., Dave, R., 2011. Simultaneous micronization and surface modification for improvement of flow and dissolution of drug particles. Int. J. Pharm. 415, 185–195.
Huang, Z., Scicolone, J.V., Gurumuthy, L., Dave, R.N., 2015a. Flow and bulk density enhancements of pharmaceutical powders using a conical screen mill: A continuous dry coating device. Chem. Eng. Sci. 125, 209–224.
Huang, Z., Scicolone, J.V., Han, X., Dave, R.N., 2015b. Improved blend and tablet properties of fine pharmaceutical powders via dry particle coating. Int. J. Pharm. 478, 447–455.
Huang, Z., Xiong, W., Kunnath, K., Bhaumik, S., Davé, R.N., 2017. Improving blend content uniformity via dry particle coating of micronized drug powders. Eur. J. Pharm. Sci. 104, 344–355.
Jivraj, M., Martini, L.G., Thomson, C.M., 2000. An overview of the different excipients useful for the direct compression of tablets. Pharm. Sci. Technol. Today 3, 58–63.
Kim, S.S., Castillo, C., Cheikhali, M., Darweesh, H., Kossor, C., Dave, R.N., 2023. Enhanced blend uniformity and flowability of low drug loaded fine API blends via dry coating: The effect of mixing time and excipient size. Int. J. Pharm. 635, 122722.
Kunnath, K., Huang, Z., Chen, L., Zheng, K., Dave, R., 2018. Improved properties of fine active pharmaceutical ingredient powder blends and tablets at high drug loading via dry particle coating. Int. J. Pharm. 543, 288–299.
Kunnath, K., Chen, L., Zheng, K., Dave, R.N., 2021. Assessing predictability of packing porosity and bulk density enhancements after dry coating of pharmaceutical powders. Powder Technol. 377, 709–722.
Kunnath, K.T., Tripathi, S., Kim, S.S., Chen, L., Zheng, K., Dave, R.N., 2023. Selection of silica type and amount for flowability enhancements via dry coating: contact mechanics based predictive approach. Pharm. Res. 1–17.
Lahdenpää, E., Niskanen, M., Yliruusi, J., 1997. Crushing strength, disintegration time and weight variation of tablets compressed from three Avicel® PH grades and their mixtures. Eur. J. Pharm. Biopharm. 43, 315–322.
Li, M., Yaragudi, N., Afolabi, A., Dave, R., Bilgili, E., 2015. Sub-100nm drug particle suspensions prepared via wet milling with low bead contamination through novel process intensification. Chem. Eng. Sci. 130, 207–220.
Lin, Z., Cabello, B., Davé, R.N., 2024. Impact of dry coating lactose as a brittle excipient on multi-component blend processability. Int. J. Pharm. 123921.
G. Mirani A., P Patankar, S., S Borole, V., S Pawar, A., J Kadam, V., Direct compression high functionality excipient using coprocessing technique: A brief review Current Drug Delivery 8 2011 426 435.
Paradkar, A., York, P., 2016. Crystal engineering and particle design for the powder compaction process. Pharmaceutical Powder Compaction Technology. CRC Press 249–266.
Pitt, K.G., Heasley, M.G., 2013. Determination of the tensile strength of elongated tablets. Powder Technol. 238, 169–175.
Rasenack, N., Müller, B.W., 2002. Crystal habit and tableting behavior. Int. J. Pharm. 244, 45–57.
Rojas, J., Buckner, I., Kumar, V., 2012. Co-proccessed excipients with enhanced direct compression functionality for improved tableting performance. Drug Dev. Ind. Pharm. 38, 1159–1170.
Rojas, J., Kumar, V., 2012. Coprocessing of cellulose II with amorphous silicon dioxide: Effect of silicification on the powder and tableting properties. Drug Dev. Ind. Pharm. 38, 209–226.
Sam, A., Fokkens, J., 1997. The drug delivery system: adding therapeutic and economic value to pharmacotherapy, Part II. Pharm. Technol. Eur. 9, 58–67.
Schulze, D., 2008. Powders and bulk solids. Behaviour, Characterization, Storage and Flow. Springer 22.
Sheth, B., Bandelin, F., Shangraw, R., 1980. Pharmaceutical Dosage Forms: Tablets. Marcel Dekker, New YorK.
Shi, L., Chattoraj, S., Sun, C.C., 2011. Reproducibility of flow properties of microcrystalline cellulose — Avicel PH102. Powder Technol. 212, 253–257.
Vanhoorne, V., Peeters, E., Van Snick, B., Remon, J.P., Vervaet, C., 2014. Crystal coating via spray drying to improve powder tabletability. Eur. J. Pharm. Biopharm. 88, 939–944.
Zheng, K., Kunnath, K., Ling, Z., Chen, L., Dave, R.N., 2020. Influence of guest and host particle sizes on dry coating effectiveness: When not to use high mixing intensity. Powder Technol. 366, 150–163.